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INVITED COMMENTARY

What to Do With Refractory Urticaria Patients

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Introduction

A urticaria patient said to be refractory to treatment ordinarily implies inadequate responsiveness to antihistamines. Thus, it is necessary to define at what point antihistamine therapy has failed. Although virtually any first-generation or second-generation antihistamine has efficacy for treatment of urticaria, few studies have compared one agent to the others, and dose-escalation studies are much in need. For the past 40 years, when first-generation antihistamines were all we had, I advocated use of hydroxyzine (Atarax; Pfizer, New York, NY) or diphenhydramine (Benadryl; McNeil-PPC, Fort Washington, PA) at doses up to 50 mg four times daily before assuming a patient to be refractory [1]. These agents ware relatively short-acting and were meant to be used in divided doses four times daily when necessary. For patients with physically induced hives such as cold urticaria or cholinergic urticaria, one could readily titrate the antihistamine dose and determine that 3 or 4 doses/d are frequently required where 1 or 2 doses do not provide adequate symptom control. Once the relatively nonsedating, second-generation, long-acting drugs were available, they were commended once daily for urticaria, as was recommended for allergic rhinitis. This turned out to be effective only in the mildest of cases of urticaria. Recently, when loratadine was tested for efficacy in the treatment of cold urticaria, it was clear that 4>3>2>1 tablets/d (ie, more is better, and side effects are minimal). In spite of the evidence of sedation with first-generation antihistamines [2–5], when they are used in high doses, sedation rapidly wears off, and they can still be recommended in countries in which second-generation agents are not available [6, 7]. There are, in fact, very few studies of sedation with use of such agents for more than a week in patients with chronic urticaria rather than in healthy volunteers. Nevertheless, for most purposes, this becomes a moot point, particularly when cost ceases to be an issue. Thus, over-the-counter generic cetirizine can be obtained inexpensively, and 6 tablets/d is roughly equivalent to hydroxyzine, 200 mg/d.

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Refractory Physically Induced Urticaria

Disorders, such as dermatographism, cold urticaria, and cholinergic urticaria, consist of individual urticarial lesions of relatively short duration (ie, a few minutes up to 2 h), and are mediated primarily by histamine. There is no late-phase reaction [7], and steroid therapy, as an alternative, is typically ineffective. When these disorders are refractory to antihistamines, there is no reliable alternative, although case reports do suggest some approaches. Omalizumab (Xolair; Genentech, South San Francisco, CA; Novartis, Basel, Switzerland) has been effective for some cases of cold urticaria [8]; whether this is globally true is not clear, but some cases have been shown to be IgE dependent [9, 10]. Thus, omalizumab might also be useful for refractory dermatographism and solar urticaria, both of which can be IgE dependent [11–15]. One exception is delayed pressure urticaria, which is generally unresponsive to any antihistamine but does respond to corticosteroids. It is characterized by delayed, long-acting hives (4–12 h after contact with the stimulus), with histology resembling that of chronic idiopathic or autoimmune urticaria [15, 16]. Thus, cyclosporine or

omalizumab could be tried as treatment of delayed pressure urticaria, and both are alternatives to corticosteroids.

Chronic Spontaneous Urticaria

This term encompasses what has been referred to as either *chronic idiopathic urticaria* or *chronic autoimmune urticaria* [17]. The latter subpopulation is associated with antibody to the IgE receptor (35%) or to IgE (5–10%) [18, 19], with an increased incidence of antithyroid antibodies (25%) [20, 21]. Refractoriness to antihistamines is defined as noted above (and here, too, 4 times/d antihistamine therapy with second-generation agents was recommended [22]); thus, the issue is what to try next. The choices in the literature would include corticosteroids, dapsone, hydroxychloroquine, methotrexate, colchicine, H_2-blockers, leukotriene antagonists, sulfasalazine, cyclosporine, and omalizumab. There are no recent blinded studies of corticosteroids, but they are clearly efficacious, although they carry many side effects, particularly when used in high doses for long periods of time [1, 7]. They are best avoided unless the dose is kept below 15 mg/d with the intent to gradually reduce and eliminate (eg, at 10 mg/d and a decrease of 1 mg/wk, the total course is 10 weeks). Double-blind, placebo-controlled studies have demonstrated remarkable efficacy of cyclosporine [23, 24], which has the potential to stop chronic urticaria in about 75% of refractory patients. Omalizumab demonstrated a similar effect in a controlled study [25] of 12 patients, all in the autoimmune subgroup; case reports [26, 27] and a study of patients lacking the autoimmune phenotype demonstrated similar efficacy [28]. All the other agents lack double-blind, placebo-controlled studies involving large numbers of patients. Basically, I never use them, but I have seen many hundreds of patients who are unresponsive to any of them. Most would undoubtedly respond to cyclosporine or omalizumab.

Conclusions

In summary, the only drugs I would recommend for refractory patients are cyclosporine, omalizumab, and low-dose corticosteroids, and combinations of these agents are possible. The others listed have such a low percentage of responders and waste so much time before we settle on a drug that works that I do not recommend any of them. For years, I routinely added H_2-receptor antagonists and leukotriene antagonists to H_1-receptor antagonists, hoping they might help and because they have virtually no side effects. Now I have concluded that the cost exceeds any efficacy and do not recommend them, either. Cyclosporine and omalizumab can dramatically alter the lives of patients with chronic urticaria and should be considered first when antihistamines fail.

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